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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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FOREWORD: This report presents the results of the bioassay of phthalamide conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that the test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals that are carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of phthalamide was conducted by the NCI Frederick Cancer Research Center (FCRC) (1), Frederick, Maryland, operated for NCI (2) by Litton Bionetics, Inc.

The manager of the bioassay at FCRC was Dr. B. Ulland, the toxicologist was Dr. E. Gordon, and Drs. R. Cardy and D. Creasia compiled the data. Ms. S. Toms was responsible for management of data, Mr. D. Cameron for management of histopathology, Mr. L. Callahan for management of the computer branch, and Mr. R. Cypher for the management of the facilities. Mr. A. Butler performed the computer services. Necropsies were performed by Drs. B. Ulland, R. Schueler, R. Ball, and R. Cardy. Histopathologic evaluations were performed by Dr. D. A. Willigan (3), and the diagnoses included in this report represent his interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (4). The statistical analyses were performed by Dr. J. R. Joiner (5) and Ms. P. L. Yong (5), using methods selected for the bioassay program by Dr. J. J. Gart (6). The chemicals used in this bioassay were analyzed at FCRG (1) by

Dr. W. Zielinsky. The chemical narrative and analyses were reviewed and approved by Dr. W. Lijinsky (1).

This report was prepared at Tracor Jitco (5) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A Owen, Ms. M. S. King, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The following scientists at NCI were responsible for evaluating the bioassay, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of phthalamide for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats of each sex were administered phthalamide at one of two doses, either 15,000 or 30,000 ppm for the males and either 5,000 or 10,000 ppm for the females, for 106 weeks. Groups of 50 mice of each sex were administered the test chemical at one of two doses, 25,000 or 50,000 ppm, for the males, and at one of three doses, 6,200, 12,500, or 25,000 ppm, for the females, for 103 or 105 weeks. Matched controls consisted of 20 untreated rats of each sex, 20 untreated male mice, and two groups of 20 untreated female mice. All surviving rats and mice were killed at the end of administration of the test chemical.

Mean body weights of the dosed groups of rats and mice were either slightly lower than those of corresponding control groups or essentially unaffected by administration of the test chemical. Also, survival was unaffected in the rats and mice except for early deaths in the high- and mid-dose groups of female mice. Survival was 66% or greater at the end of the bioassay in all dosed and control groups of each species and sex except for the high-dose group of female mice (36%). With the exception of the high-dose female mice, sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups. However, phthalamide produced toxic lesions in the livers of male and female rats and the urinary systems of female rats and mice. The presence of nonneoplastic lesions suggests that the MTD may have been used or exceeded.

It is concluded that under the conditions of this bioassay, phthalamide was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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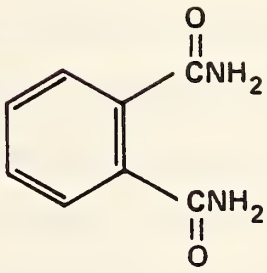
I. INTRODUCTION

Phthalamide, o-phthalic acid diamide, or P-D (CAS 88-96-0; NCI C03612) is recommended for use as an accelerator for curing epoxy resins. It is believed to be used chiefly in the paint industry (Sherwin Williams, personal communication, 1978; Clelford and Coulter, 1969).



Phthalamide

Phthalamide was selected as a representative phthalic acid derivative for evaluation of possible carcinogenicity by the National Cancer Institute.

II. Materials and Methods

A. Chemical

Phthalamide (o-phthalic acid diamide) was obtained from Sherwin Williams Chemicals as a fine, white powder. Elemental analysis showed mean values of 58.3% carbon, 4.9% hydrogen, and 17.3% nitrogen (theoretical: 58.5% C, 4.9% H, and 17.1% N). Its infrared spectrum was consistent with its chemical structure and was identical to that of a reference standard of phthalamide. Mass spectral analysis showed a molecular ion at m/e 164 and a base peak at m/e 148. Proton NMR analysis confirmed the structure of phthalamide and showed no peaks due to impurities. Analysis at two different wavelengths indicated that the effluent from high-pressure liquid chromatography contained three components one of which was greater than 99%, with two minor contaminants. Thin-layer chromatography of the material gave only one detectable spot.

The test material was stored at $5^{o}C$ until used.

B. Dietary Preparation

Test diets containing phthalamide were prepared fresh every 1 to 1-1/2 weeks in 6- to 12-kg batches at the appropriate doses. A known weight of the chemical was first mixed with an equal weight of autoclaved Wayne® Sterilizable Lab Meal with 4% fat (Allied Mills, Inc., Chicago, Ill.), using a mortar and pestle. The mixing was continued with second and third additions of feed, and final mixing was performed with the remaining quantity of feed for a minimum of 15 minutes in a Patterson-Kelly twin-shell blender. The diets were routinely stored at 5°C until used.

C. Animals

Male and female F344 (Fischer) rats and B6C3F1 mice were obtained as 4-week-old weanlings, all within 3 days of the same age, from the NCI Frederick Cancer Research Center (Frederick, Md.). The animals were housed within the test facility for 2 weeks and were then assigned four rats to a cage and five mice to a cage on a weight basis for each cage of animals of a given species and sex. Male rats used in the chronic study weighed 90 to 105 g, averaging at least 100 g; the female rats, 80 to 95 g, averaging at

least 90 g; the male mice, 18 to 22 g, averaging at least 19.5 g; and the female mice, 17 to 21 g, averaging at least 18.5 g. Individual animals were identified by ear punch.

D. Animal Maintenance

The animals were housed in polycarbonate cages (Lab Products Inc., Garfield, N. J.), 19 x 10-1/2 x 8 inches for the rats and 11-1/2 x 7-1/2 x 5 inches for the mice. The cages were suspended from aluminum racks (Scientific Cages, Inc., Bryan, Tex.) and were covered by nonwoven polyester-fiber 12-mil-thick filter paper (Hoeltge, Inc., Cincinnati, Ohio). The bedding used was Absorb-dri® hardwood chips (Northeastern Products, Inc., Warrenburg, N. Y). The feed supplied was presterilized Wayne® Sterilizable Lab Meal with 4% fat, provided *ad libitum* in suspended stainless steel hoppers and replenished as required, at least three times per week. Water, acidified to pH 2.5, was supplied *ad libitum* from glass bottles with sipper tubes suspended through the tops of the cages.

The contaminated bedding was disposed of through an enclosed vacuum line that led to a holding tank from which the bedding was fed periodically into an incinerator. The cages were sanitized

twice per week and the feed hoppers twice per month at 82 to 88°C in a tunnel-type cagewasher (Industrial Washing Machine Corp., Mataway, N. J.), using the detergents, Clout® (Pharmacal Research Laboratories, Greenwich, Conn.) or Oxford D'Chlor (Oxford Chemicals, Atlanta, Ga.). The glass bottles and sipper tubes were sanitized at 82 to 88°C in a tunnel-type bottle washer (Consolidated Equipment Supply Co., Mercersburg, Pa.) three times per week, using a Calgen Commercial Division detergent (St. Louis, Mo.). The racks for the cages were sanitized at or above 82°C in a rack washer (Consolidated Equipment Co.) once per month, using the Calgen Commercial Division detergent, and the filter paper was changed at the same time.

The animal rooms were maintained at 22 to 24°C and 45 to 55% relative humidity. Incoming air was passed through a filter of 65% efficiency and a bag filter of 95% efficiency at the intake and was expelled without recirculation through a "Z"-type roughing filter of 30% efficiency and a bag system of 90 to 95% efficiency at the exhaust (American Air Filters, Louisville, Ky.; Mine Safety Appliances, Pittsburgh, Pa.). Room air was changed 15 times per hour. The air pressure was maintained negative to a clean hallway and positive to a return hallway. Fluorescent lighting was provided automatically on a 12-hour-per-day cycle.

Rats administered phthalamide and their corresponding controls were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 128-37-0) butylated hydroxytoluene (BHT)
(CAS 137-17-7) 2,4,5-trimethylaniline

Mice administered phthalamide and their corresponding controls were housed in the same room as mice on feeding studies of the following chemicals:

(CAS 156-62-7) calcium cyanamide
(CAS 999-81-5) (2-chloroethyl)trimethylammonium chloride (CCC)
(CAS 95-80-7) 2,4-diaminotoluene
(CAS 19010-66-3) lead dimethyldithiocarbamate
(CAS 86-30-6) N-nitrosodiphenylamine
(CAS 120-62-7) piperonyl sulfoxide
(CAS 137-17-7) 2,4,5-trimethylaniline

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of phthalamide, on the basis of which two concentrations (referred to in this report as "low" and "high" doses) were selected for administration in the chronic studies. Groups of five rats and five mice of each sex were fed diets containing phthalamide for 7 weeks, followed by 1 week of additional observation; groups of five control animals of each sex and species were administered basal diet only. Each animal

was weighed twice per week. Table 1 shows the number of animals in each dosed group that survived during the course of administration and the mean body weights of dosed animals at week 7, expressed as percentages of mean body weights of the controls.

At the end of the subchronic studies, all animals were killed using CO_2 and necropsied. Clinical signs and histopathologic findings are included in table 1 as footnotes.

In the rats, ten percent depression in body weight was a major criterion for selection of the MTD. The doses required to produce this response were determined by the following procedure: first, least squares regressions of mean body weights versus days on study were used to estimate mean body weights of each of the dosed groups at day 49. Next, probits of the percent weights of dosed groups at day 49 relative to weights of corresponding control groups were plotted against the logarithms of the doses, and least squares regressions fitted to the data were used to estimate the doses required to induce 10% depression in weight. In the mice, there was no effect on weights and the doses were set at the maximum amount allowed for use in the Carcinogenicity Testing Program.

The low and high doses for the chronic studies were set at 15,000

Table 1. Phthalamide Subchronic Feeding Studies in Rats and Mice

	Male		Female	
Dose (ppm)	Survival(a)	Mean Weight at Week 7 as % of Control	Survival(a)	Mean Weight at Week 7 as % of Control
RATS				
6,200	5/5	99	5/5	98
12,500 (b,c)	5/5	86	5/5	96
25,000 (d)	5/5	87	3/5	70
50,000 (b,d)	5/5	90	0/5	
MICE				
6,200	5/5	120	5/5	102
12,500	4/5	120	5/5	111
25,000 (c)	5/5	107	5/5	105
50,000 (b)	5/5	111	0/5	

(a) Number surviving/number in group.

(b) The tissues of male rats and mice at these doses were examined histopathologically and were found to be essentially normal.

(c) The tissues of female rats and mice at these doses were examined histopathologically and were found to be essentially normal.

(d) Clinical signs in female rats included arched back and rough hair.

and 30,000 ppm for male rats and 5,000 and 10,000 ppm for female rats. For mice, the low and high doses for the chronic studies were set at 25,000 and 50,000 ppm for males and 12,500 and 25,000 ppm for females.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 2 and 3. Due to early deaths in the initial groups of female mice, a group of 50 female mice dosed at 6,200 ppm, together with a group of 20 additional control animals, was placed on study at week 9, as shown in table 3.

G. Clinical and Pathologic Examinations

All animals were observed twice daily. Observations for sick, tumor-bearing, and moribund animals were recorded daily. Clinical examination and palpation for masses were performed each month, and the animals were weighed at least once per month. Moribund animals and those that survived to the end of the bioassay were killed using CO_2 and necropsied.

Table 2. Phthalamide Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals(a)	Phthalamide in Diet(b) (ppm)	Time on Study (weeks)
Male			
Matched-Control	20	0	106
Low-Dose	50	15,000	106
High-Dose	50	30,000	106
Female			
Matched-Control	20	0	106
Low-Dose	50	5,000	106
High-Dose	50	10,000	106

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided *ad libitum* 7 days per week.

Table 3. Phthalamide Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals(a)	Phthalamide in Diet(b) (ppm)	Time on Study (weeks)
Male			
Matched-Control	20	0	105
Low-Dose	50	25,000	105
High-Dose	50	50,000	105
Female			
Low-Dose Control	20(c)	0	103
Mid- and High-Dose Control	20	0	105
Low-Dose	50(c)	6,200	103
Mid-Dose	50	12,500	105
High-Dose	50	25,000	105

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided *ad libitum* 7 days per week.

(c) The group of 50 female mice dosed at 6,200 ppm was placed on study at week 9, together with 20 additional control animals (low-dose control), because of early deaths in the initial group of high-dose female mice.

Gross and microscopic examinations of major tissues, major organs, and all gross lesions were performed. The tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (parotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, mammary gland, uterus, ovary, brain (cerebrum and cerebellum), and all tissue masses. Peripheral blood smears also were made for all animals, whenever possible.

Necropsies were also performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the appropriate statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative section.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for

a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each

dose level. When results for a number of dosed groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When

such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity (P less than 0.05, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true

binomial probability of the incidence of a specific type of tumor in a dosed group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a dosed group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the dosed group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of

the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of the low- and high-dose male rats were only slightly lower than those of the corresponding controls (figure 1). Mean body weights of the low-dose females were essentially unaffected by administration of the test chemical throughout the bioassay; mean body weights of the high-dose females were lower than those of the corresponding controls only after week 70. Fluctuation in the growth curve may be due to mortality; as the size of a group diminishes the mean body weight may be subject to wide variation. Incidences of tissue masses and of wasting were higher in the dosed groups of males and females than in corresponding control groups.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered phthalamide in the diet at the doses of this bioassay, together with those for the matched controls, are shown by the Kaplan and Meier curves in figure 2. The result of the

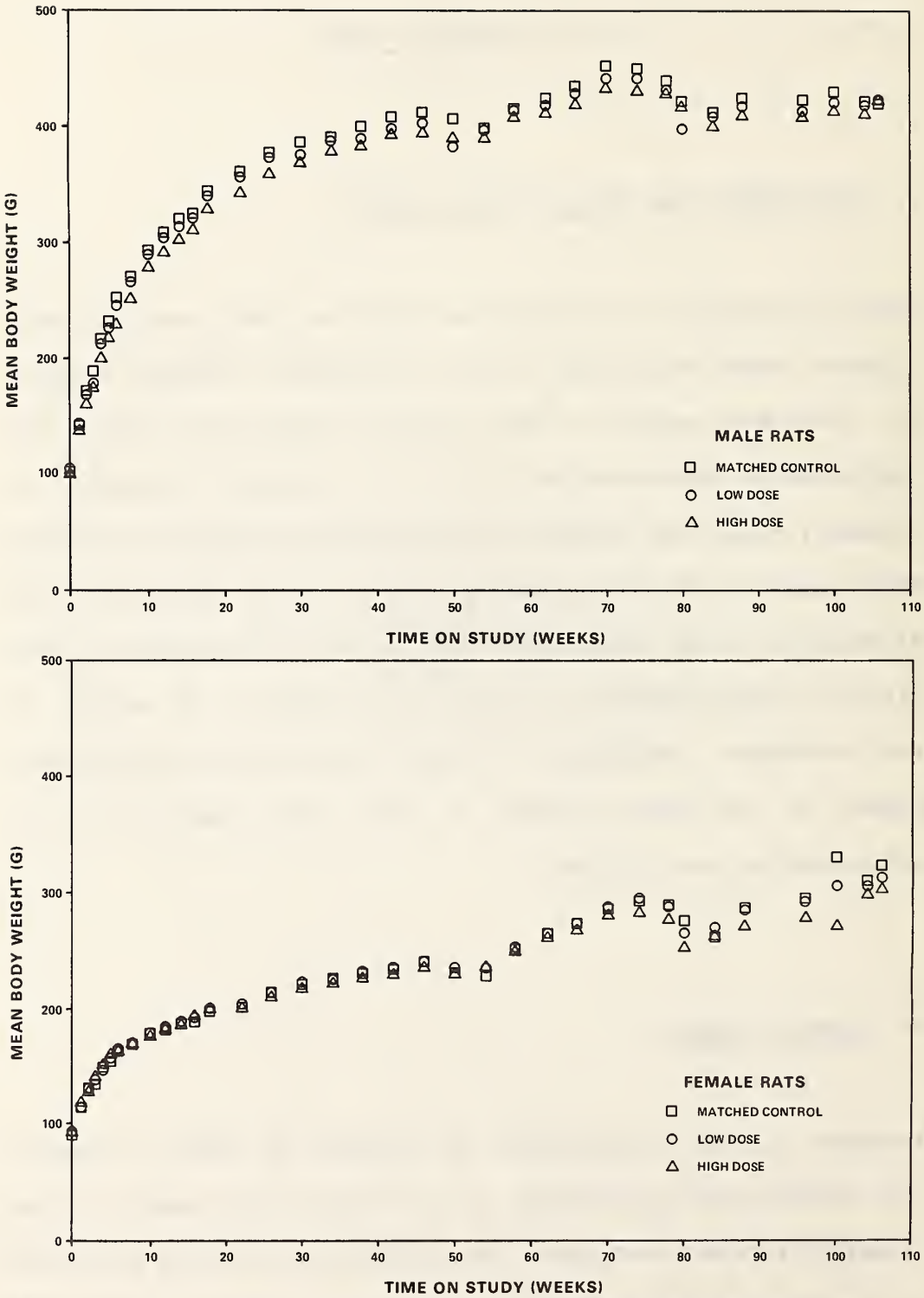


Figure 1. Growth Curves for Rats Administered Phthalamide in the Diet

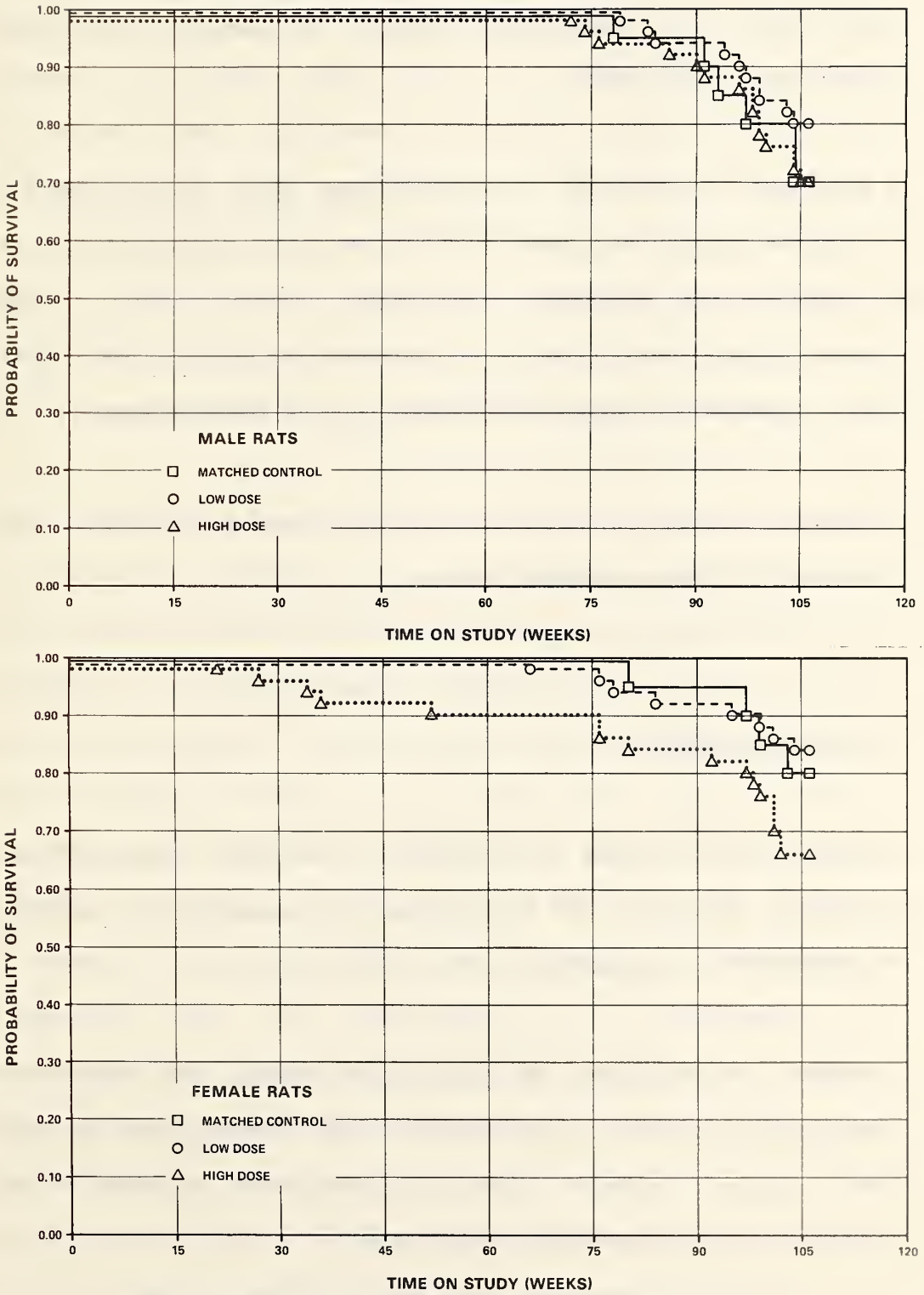


Figure 2. Survival Curves for Rats Administered Phthalamide in the Diet

Tarone test for dose-related trend in mortality is not significant in either sex.

In male rats, 35/50 (70%) of the high-dose group, 40/50 (80%) of the low-dose group, and 14/20 (70%) of the control group lived to the end of the bioassay. In females, 33/50 (66%) of the high-dose group, 42/50 (84%) of the low-dose group, and 16/20 (80%) of the control group lived to the end of the bioassay.

Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, tables C1 and C2.

A variety of neoplasms are represented among the dosed and control groups of rats. Each type has been commonly seen in aged F344 rats and occurred with no appreciable difference in frequency between control and dosed rats.

Hepatocellular carcinomas and neoplastic nodules of the liver occurred in the dosed groups, but the incidences were low and were probably not significantly different from those of the controls; however, fatty metamorphosis of the liver in the male rats (controls 1/20, low-dose 15/50, high-dose 11/50) and chronic pericholangiolitis, coded in Appendix C, table C2, as cholangiofibrosis, in the females (controls 0/20, low-dose 7/50, high-dose 4/49) appeared related to administration of the test chemical.

A variety of nonneoplastic lesions other than those cited above in the liver are represented among both control and dosed groups of rats. Most of these have been encountered previously and are considered to be those commonly observed in aging F344 rats; however, pyelonephritis (controls 1/20, low-dose 0/50, high-dose 9/50) and cystitis (controls 1/18, low-dose 0/49, high-dose 7/50) occurred in the high-dose females. The inflammatory changes involving the urinary bladder mucosa in the high-dose females were usually associated with mucosal hyperplasia (7/50) and infrequently with the development of transitional-cell papillomas, coded in Appendix A, table A2, as adenomatous polyps (1/50) and transitional-cell carcinoma with some squamous differentiation, coded in Appendix A, table A2, as adenocarcinomas (2/50). Urinary bladders of the low-dose females and of both the low- and high-dose males were unaffected.

The histopathologic examination provided no conclusive evidence of carcinogenicity under the conditions of this bioassay; however, phthalamide may have induced inflammatory and proliferative lesions of the bladder and inflammatory and degenerative lesions of the liver in F344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

The results of the Cochran-Armitage test for dose-related trend in the incidences of tumors and the results of the Fisher exact test comparing the incidences of tumors in the control group with those in each dosed group are not significant in the positive direction. However, significant results in the negative direction are observed in the incidences of lung tumors and hematopoietic tumors in male rats and the incidences of adenomas of the pituitary in both male and female rats.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals, except that for the incidence of lung tumors in the high-dose male rats, has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by phthalamide, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the low- and high-dose male mice were slightly lower than those of the corresponding controls throughout the bioassay (figure 3). Mean body weights of the low-dose females were consistently lower than those of the corresponding low-dose controls although the mean body weights of the mid- and high-dose females did not show consistent differences from those of the mid- and high-dose controls. Fluctuation in the growth curve may be due to mortality; as the size of a group diminishes the mean body weight may be subject to wide variation. Corneal opacity occurred in the high-dose females at an incidence that was higher than the incidences in any other dosed or control groups. Tissue masses occurred at comparable incidences in dosed and control groups.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered phthalamide in the diet at the doses of this

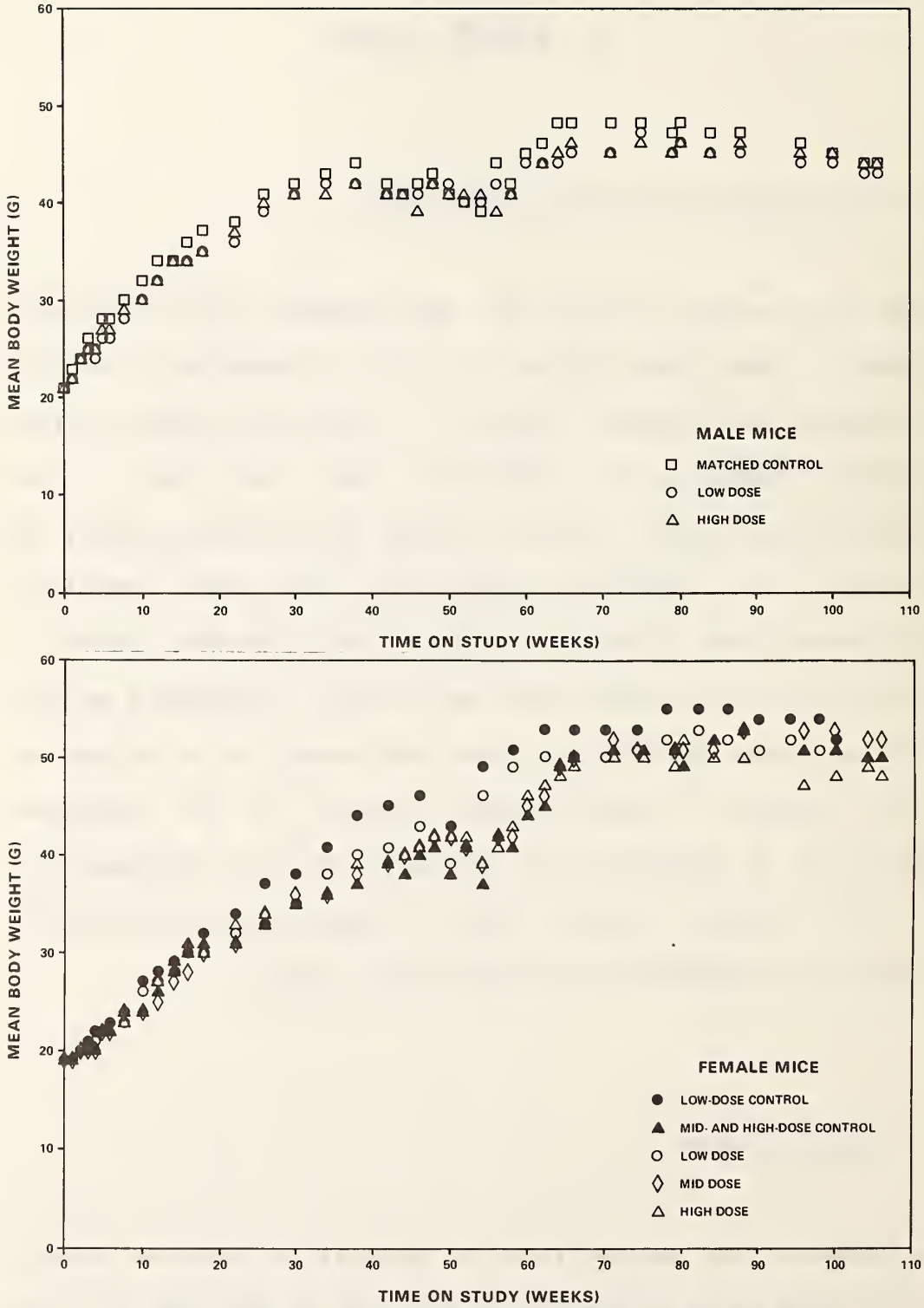


Figure 3. Growth Curves for Mice Administered Phthalamide in the Diet

bioassay, together with those for the matched controls, are shown by the Kaplan and Meier curves in figure 4. The result of the Tarone test for dose-related trend in mortality of the males is not significant. In females, there are five groups: three dosed groups (high-, mid-, and low-dose) of 50 animals each and two matched-control groups of 20 animals each. The low-dose group and one control group (low-dose control) were started on study 9 weeks later than the other three groups (see table 3, above). The statistical analysis in this report combined the two control groups, and the Tarone test for dose-related trend in mortality is applied as if all groups were started on study at the same time. The result of the Tarone test for dose-related trend in mortality of the females is significant (P less than 0.001). An indicated departure from linear trend is observed (P less than 0.001), due to the relatively steep decrease in survival among the high- and mid-dose animals.

In male mice, 37/50 (74%) of the high-dose group, 35/50 (70%) of the low-dose group, and 18/20 (90%) of the control group lived to the end of the bioassay. In females, 18/50 (36%) of the high-dose group, 33/50 (66%) of the mid-dose group, 41/50 (82%) of the low-dose group, and 32/40 (80%) of the combined control group lived to the end of the bioassay.

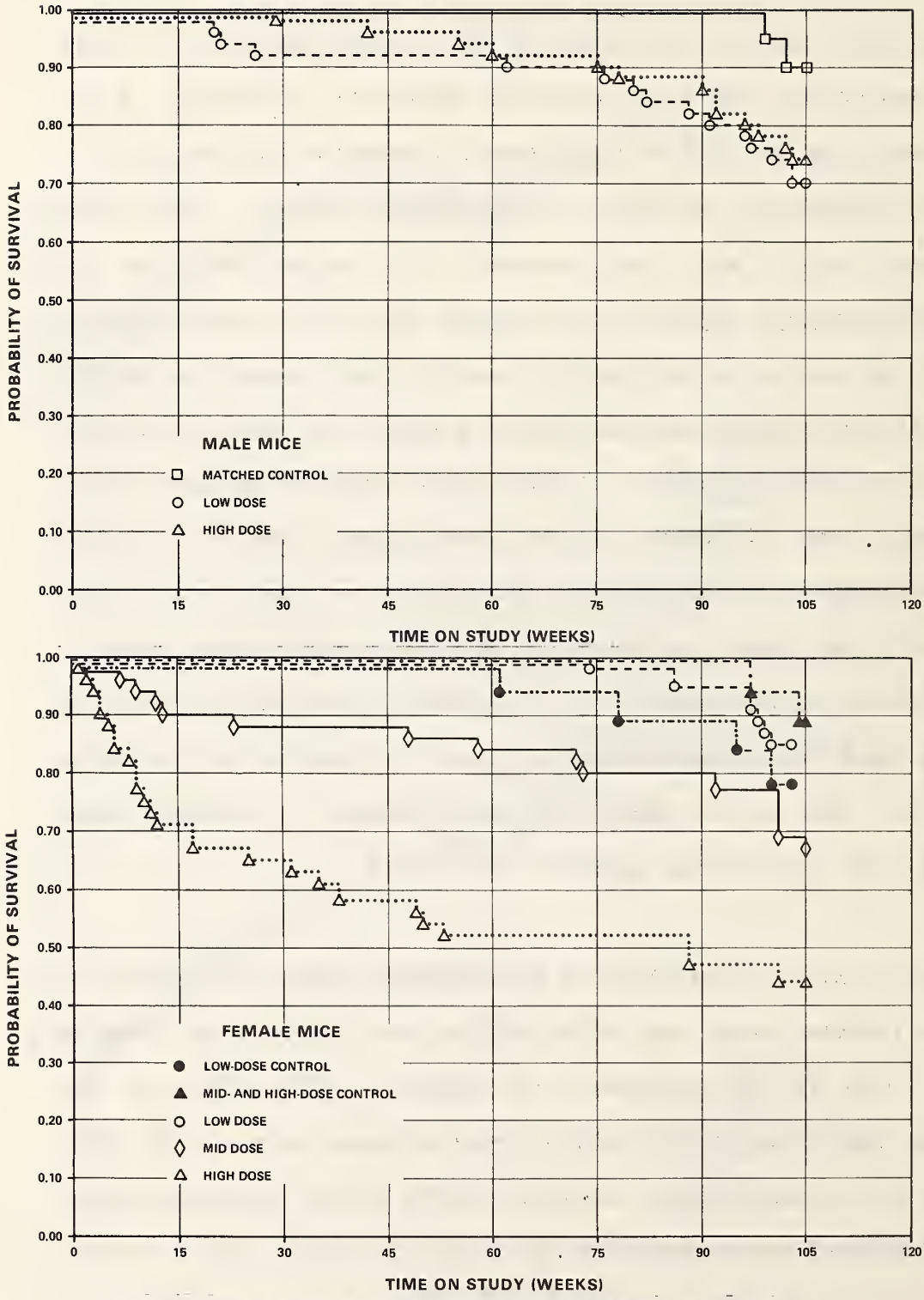


Figure 4. Survival Curves for Mice Administered Phthalamide in the Diet

Except for the high-dose female mice, in which there were large numbers of early deaths, sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, tables D1 and D2.

A variety of neoplasms are represented among the dosed and control groups of mice. Each type has been encountered previously as a spontaneous lesion in the B6C3F1 mouse and occurred with no appreciable difference in frequency between control and dosed mice.

A variety of nonneoplastic responses also are represented among the control and dosed groups of mice. Such lesions have been encountered previously and are similar to those commonly observed in aging B6C3F1 mice. The incidence and type of lesion are without relationship to exposure to the test chemical, except for urinary-tract lesions, which occurred only in dosed animals. Crystals occurred in the urinary bladders of 17/44 high-dose and

5/46 mid-dose female mice; a few occurred in dosed males. Mucosal hyperplasia was seen in 3/44 high-dose and 4/46 mid-dose female mice and a few dosed male mice. Obstructive nephropathy was noted in 14/48 high-dose and 4/49 mid-dose females and in one dosed and one control male.

This histopathologic examination provided no evidence for the carcinogenicity of phthalamide in B6C3F1 mice under the conditions of the bioassay. However, nonneoplastic renal and bladder lesions were induced in the female mice.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In male mice, the two dosed groups and their corresponding matched-control group were all started on study at the same time. In females, however, the low-dose group and one matched-control group were started on study 9 weeks later than the other three groups (see table 3, above). For statistical analysis, the

female control groups are combined, and the Cochran-Armitage test for dose-related trend in incidence of tumors is applied as if all groups were started on study at the same time. Due to the early mortality of the high-dose animals, the Cochran-Armitage test is also made using only the combined control, low-, and mid-dose groups, excluding the high-dose group. Both results are reported in the statistical table F2.

In male mice, the results of the Cochran-Armitage test for dose-related trend in the incidences of tumors and the results of the Fisher exact test comparing the incidence of tumors in the control group with those in each dosed group are not significant in the positive direction. A significant trend in the negative direction is observed in the incidence of hepatocellular carcinomas, but when the incidence of male mice with either hepatocellular carcinoma or adenoma is analyzed, no significant trend is observed.

In female mice, the results of the Fisher exact test comparing the incidences of tumors in the control group with those in each dosed group are not significant in the positive direction. Significant trends in the negative direction are observed in the incidences of lung tumors, liver tumors, and adenomas of the pituitary, when the Cochran-Armitage test is applied to the

control, low-, mid-, and high-dose groups. This significance in the negative direction may be accounted for by the early mortality of the high-dose female mice. When the Cochran-Armitage test is applied, excluding the incidence in the high-dose group, a significant (P = 0.042) trend in the positive direction is observed in the incidence of hematopoietic tumors. However, when the life-table method is applied to the incidences of hematopoietic tumors in female mice, excluding the incidences in the high-dose group, the result of the Tarone test for dose-related trend is not significant.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals, except that for the incidence of liver tumors in the high-dose female mice, has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by phthalamide, which could not be detected under the conditions of this test.

V. DISCUSSION

Mean body weights of the dosed groups of rats and mice were either slightly lower than those of corresponding control groups or were essentially unaffected by administration of the phthalamide. Also, survival was unaffected in the rats and mice except for early deaths in the high- and mid-dose groups of female mice. Survival was 66% or greater at the end of the bioassay in all dosed and control groups of each species and sex except for the high-dose group of female mice (36%). Except for these high-dose female mice, sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups. The presence of nonneoplastic lesions suggests that the MTD may have been used or exceeded. Fatty metamorphosis of the liver in the male rats, chronic pericholangiolitis, pyelonephritis, cystitis, and bladder mucosal hyperplasia in the female rats, and cystitis, bladder mucosal hyperplasia, and obstructive nephropathy in the female mice may each have been related to administration of the test chemical.

No previous studies on the possible carcinogenicity of phthalamide have been identified.

It is concluded that under the conditions of this bioassay, phthalamide was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED PHTHALAMIDE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED PHTHALAMIDE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
PAPILLOMA, NOS			2 (4%)
SQUAMOUS CELL CARCINOMA		1 (2%)	
KERATOACANTHOMA		2 (4%)	
*SUBCUT TISSUE	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
SARCOMA, NOS			1 (2%)
FIBROMA		1 (2%)	2 (4%)
FIBROSARCOMA		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (15%)	3 (6%)	
FOLLICULAR-CELL CARCINOMA, METAS			1 (2%)
LEIOMYOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	6 (30%)	9 (18%)	5 (10%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)	1 (2%)	1 (2%)
LEUKEMIA,NOS			1 (2%)
MONOCYTIC LEUKEMIA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		
#BONE MARROW	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#CERVICAL LYMPH NODE	(20)	(49)	(48)
FOLLICULAR-CELL CARCINOMA, METAS			1 (2%)
#MEDIASTINAL L.NODE	(20)	(49)	(48)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
#MESENTERIC L. NODE	(20)	(49)	(48)
HEMANGIOMA			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
NEOPLASTIC NODULE			1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)	1 (2%)
LEIOMYOSARCOMA, METASTATIC		1 (2%)	
#PANCREAS	(20)	(49)	(49)
ACINAR-CELL ADENOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(49)	(49)
ADENOMA, NOS	3 (17%)	4 (8%)	1 (2%)
CHROMOPHOBE ADENOMA	3 (17%)	16 (33%)	9 (18%)
CHROMOPHOBE CARCINOMA	1 (6%)	2 (4%)	8 (16%)
#ADRENAL	(20)	(50)	(50)
PHEOCHROMOCYTOMA	4 (20%)	11 (22%)	11 (22%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMANGIOSARCOMA		1 (2%)	
#THYROID	(19)	(50)	(48)
FOLLICULAR-CELL ADENOMA	1 (5%)		
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA		3 (6%)	6 (13%)
C-CELL CARCINOMA		1 (2%)	
CYSTADENOMA, NOS		1 (2%)	
#PANCREATIC ISLETS	(20)	(49)	(49)
ISLET-CELL ADENOMA	1 (5%)		2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
LIPOMA		1 (2%)	
FIBROADENOMA		1 (2%)	1 (2%)
#TESTIS	(20)	(50)	(50)
INTERSTITIAL-CELL TUMOR	1 (5%)	3 (6%)	3 (6%)
INTERSTITIAL-CELL TUMOR, MALIGNA	17 (85%)	41 (82%)	37 (74%)
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	2 (4%)
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	8	10
MORIBUND SACRIFICE	3	2	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	40	35
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	50	48
TOTAL PRIMARY TUMORS	42	110	100
TOTAL ANIMALS WITH BENIGN TUMORS	14	33	29
TOTAL BENIGN TUMORS	16	47	38
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	46	44
TOTAL MALIGNANT TUMORS	26	62	58
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1
TOTAL SECONDARY TUMORS		3	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	4
TOTAL UNCERTAIN TUMORS		1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED PHTHALAMIDE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
BASAL-CELL CARCINOMA	1 (5%)		
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA		2 (4%)	
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	3 (15%)	4 (8%)	4 (8%)
LEUKEMIA,NOS			2 (4%)
MONOCYTIC LEUKEMIA	1 (5%)	1 (2%)	
#MESENTERIC L. NODE	(18)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (6%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(49)	(48)
CYSTADENOMA, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(20)	(50)	(49)
NEOPLASTIC NODULE	2 (10%)	2 (4%)	6 (12%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
FIBROADENOMA		1 (2%)	
#URINARY BLADDER	(18)	(49)	(50)
ADENOCARCINOMA, NOS (a)			2 (4%)
ADENOMATOUS POLYP, NOS (b)			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(50)	(48)
ADENOMA, NOS	3 (16%)	2 (4%)	1 (2%)
ADENOCARCINOMA, NOS		3 (6%)	1 (2%)
CHROMOPHOBE ADENOMA	5 (26%)	23 (46%)	22 (46%)
CHROMOPHOBE CARCINOMA		2 (4%)	2 (4%)
#ADRENAL	(20)	(50)	(50)
CORTICAL ADENOMA		1 (2%)	
PHEOCHROMOCYTOMA			2 (4%)
#THYROID	(20)	(50)	(48)
C-CELL ADENOMA	1 (5%)	5 (10%)	2 (4%)
CYSTADENOMA, NOS	1 (5%)		1 (2%)
#THYROID FOLLICLE	(20)	(50)	(48)
CYSTADENOMA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS		2 (4%)	1 (2%)
ADENOCARCINOMA, NOS		1 (2%)	
CYSTADENOMA, NOS		1 (2%)	3 (6%)
FIBROADENOMA	3 (15%)	10 (20%)	9 (18%)
CYSTFIBROADENOMA			1 (2%)
NERVOUS SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

(a) TRANSITIONAL-CELL CARCINOMA

(b) TRANSITIONAL-CELL PAPILLOMA

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	5	10
MORIBUND SACRIFICE	1	3	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	42	33
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	39	39
TOTAL PRIMARY TUMORS	22	62	62
TOTAL ANIMALS WITH BENIGN TUMORS	12	33	32
TOTAL BENIGN TUMORS	14	48	44
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	12	10
TOTAL MALIGNANT TUMORS	6	12	11
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	2	7
TOTAL UNCERTAIN TUMORS	2	2	7
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED PHTHALAMIDE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED PHTHALAMIDE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
CYSTADENOMA, NOS			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROUS HISTIOCYTOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (15%)	7 (14%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		5 (10%)	5 (10%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (10%)		1 (2%)
#BONE MARROW	(20)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)
#SPLEEN	(20)	(49)	(50)
HEMANGIOMA		1 (2%)	1 (2%)
HEMANGIOSARCOMA	1 (5%)		1 (2%)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#MESENTERIC L. NODE	(20)	(50)	(46)
HEMANGIOMA		2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, NOS			3 (7%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PEYERS PATCH	(20)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
*MESENTERY	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#THYMUS	(12)	(30)	(33)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
BILE DUCT CARCINOMA			1 (2%)
HEPATOCELLULAR ADENOMA	1 (5%)	5 (10%)	5 (10%)
HEPATOCELLULAR CARCINOMA	8 (40%)	12 (24%)	9 (18%)
HEMANGIOSARCOMA			1 (2%)
#CECUM	(20)	(49)	(49)
HEMANGIOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(20)	(49)	(45)
CORTICAL ADENOMA		2 (4%)	1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	2 (4%)
#THYROID	(19)	(48)	(50)
ADENOCARCINOMA, NOS			1 (2%)
#PANCREATIC ISLETS	(20)	(50)	(49)
ISLET-CELL ADENOMA	2 (10%)	1 (2%)	6 (12%)
REPRODUCTIVE SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(20)	(50)	(50)
PAPILLARY ADENOMA	1 (5%)	2 (4%)	
PAPILLARY CYSTADENOMA, NOS	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
SARCOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
SARCOMA, NOS, METASTATIC		1 (2%)	
HEMANGIOMA		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	15	13
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	35	37
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	15	33	32
TOTAL PRIMARY TUMORS	20	44	52
TOTAL ANIMALS WITH BENIGN TUMORS	8	18	21
TOTAL BENIGN TUMORS	9	22	26
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	19	19
TOTAL MALIGNANT TUMORS	11	22	26
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	
TOTAL SECONDARY TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED PHTHALAMIDE IN THE DIET

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
ANIMALS MISSING			1	1	2
ANIMALS NECROPSIED	20	20	49	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	20	49	49	48
INTEGUMENTARY SYSTEM					
*SKIN	(20)	(20)	(49)	(49)	(48)
ADNEXAL CARCINOMA					1 (2%)
HEMANGIOMA			1 (2%)		
*SUBCUT TISSUE	(20)	(20)	(49)	(49)	(48)
HEMANGIOMA			1 (2%)		
RESPIRATORY SYSTEM					
#LUNG	(20)	(20)	(48)	(49)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	2 (10%)	5 (10%)	1 (2%)	
ADNEXAL CARCINOMA, METASTATIC					1 (2%)
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(20)	(20)	(49)	(49)	(48)
MALIGNANT LYMPHOMA, NOS	2 (10%)	2 (10%)	3 (6%)	6 (12%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)	5 (10%)	5 (10%)	1 (2%)
*HEMATOPOIETIC SYSTEM	(20)	(20)	(49)	(49)	(48)
MALIGNANT LYMPHOMA, NOS			1 (2%)		
GRANULOCYTIC LEUKEMIA	1 (5%)				
#BONE MARROW	(20)	(20)	(49)	(49)	(47)
HEMANGIOMA		1 (5%)	1 (2%)	1 (2%)	
HEMANGIOSARCOMA				1 (2%)	
#CERVICAL LYMPH NODE	(20)	(20)	(48)	(47)	(47)
HEMANGIOSARCOMA				1 (2%)	
#MESENTERIC L. NODE	(20)	(20)	(48)	(47)	(47)
MALIGNANT LYMPHOMA, NOS			1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				2 (4%)	1 (2%)
#LIVER	(20)	(20)	(49)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)		
#PEYERS PATCH	(20)	(20)	(48)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				3 (6%)	
#KIDNEY	(20)	(20)	(49)	(49)	(48)
MALIGNANT LYMPHOMA, NOS		1 (5%)			
*VAGINA	(20)	(20)	(49)	(49)	(48)
GRANULOCYTIC SARCOMA				1 (2%)	
#THYMUS	(11)	(17)	(43)	(37)	(43)
MALIGNANT LYMPHOMA, NOS			1 (2%)	1 (3%)	
CIRCULATORY SYSTEM					
NONE					
DIGESTIVE SYSTEM					
#LIVER	(20)	(20)	(49)	(49)	(48)
HEPATOCELLULAR ADENOMA	4 (20%)		1 (2%)	1 (2%)	
HEPATOCELLULAR CARCINOMA			1 (2%)	1 (2%)	
HEMANGIOMA	1 (5%)				
#CARDIAC STOMACH	(20)	(20)	(49)	(48)	(48)
SQUAMOUS CELL PAPILLOMA				1 (2%)	
URINARY SYSTEM					
NONE					
ENDOCRINE SYSTEM					
#PITUITARY	(20)	(18)	(46)	(47)	(41)
ADENOMA, NOS	5 (25%)	2 (11%)	11 (24%)	5 (11%)	3 (7%)
#ADRENAL	(20)	(20)	(49)	(49)	(47)
CORTICAL ADENOMA				1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
PHEOCHROMOCYTOMA				2 (4%)	
#THYROID	(20)	(19)	(46)	(47)	(48)
FOLLICULAR-CELL ADENOMA	1 (5%)				
#PANCREATIC ISLETS	(20)	(20)	(47)	(49)	(48)
ISLET-CELL CARCINOMA			1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(20)	(20)	(49)	(49)	(48)
ADENOCARCINOMA, NOS			1 (2%)		
#OVARY	(19)	(20)	(48)	(47)	(44)
PAPILLARY ADENOMA					2 (5%)
PAPILLARY CYSTADENOMA, NOS		1 (5%)			
EMBRYONAL CARCINOMA				1 (2%)	
NERVOUS SYSTEM					
NONE					
SPECIAL SENSE ORGANS					
*EYE/LACRIMAL GLAND	(20)	(20)	(49)	(49)	(48)
PAPILLARY ADENOMA			1 (2%)		
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
NONE					
ALL OTHER SYSTEMS					
NONE					

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
NATURAL DEATH@	4	2	5	16	24
MORIBUND SACRIFICE			2		2
SCHEDULED SACRIFICE					
ACCIDENTALLY KILLED	1	1	1		4
TERMINAL SACRIFICE	15	17	41	33	18
ANIMAL MISSING			1	1	2
@ INCLUDES AUTOLYZED ANIMALS					
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	8	29	27	8
TOTAL PRIMARY TUMORS	15	10	36	35	9
TOTAL ANIMALS WITH BENIGN TUMORS	9	5	19	12	5
TOTAL BENIGN TUMORS	12	6	21	12	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	4	15	22	4
TOTAL MALIGNANT TUMORS	3	4	15	23	4
TOTAL ANIMALS WITH SECONDARY TUMORS#					1
TOTAL SECONDARY TUMORS					1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT					
TOTAL UNCERTAIN TUMORS					
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC					
TOTAL UNCERTAIN TUMORS					

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED PHTHALAMIDE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED PHTHALAMIDE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
ABSCESS, CHRONIC		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
CONGESTION, NOS	1 (5%)	1 (2%)	3 (6%)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (5%)	1 (2%)	
#LUNG/ALVEOLI	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(50)	(50)
HEMORRHAGE			1 (2%)
HYPERPLASIA, GRANULOCYTIC	2 (10%)	3 (6%)	2 (4%)
HYPOPLASIA, HEMATOPOIETIC		1 (2%)	3 (6%)
#SPLEEN	(20)	(50)	(50)
CONGESTION, NOS		1 (2%)	1 (2%)
HEMOSIDEROSIS			8 (16%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID		4 (8%)	1 (2%)
HEMATOPOIESIS			2 (4%)
#LYMPH NODE	(20)	(49)	(48)
LYMPHANGIECTASIS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, LYMPHOID		1 (2%)	
#CERVICAL LYMPH NODE	(20)	(49)	(48)
LYMPHANGIECTASIS	5 (25%)	14 (29%)	14 (29%)
CONGESTION, NOS	1 (5%)	2 (4%)	1 (2%)
PLASMA-CELL INFILTRATE			1 (2%)
HEMOSIDEROSIS	1 (5%)		
ERYTHROPHAGOCYTOSIS			1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (5%)		1 (2%)
HYPERPLASIA, LYMPHOID		3 (6%)	2 (4%)
#HEPATIC LYMPH NODE	(20)	(49)	(48)
CONGESTION, NOS		1 (2%)	
#MESENTERIC L. NODE	(20)	(49)	(48)
LYMPHANGIECTASIS	1 (5%)	2 (4%)	3 (6%)
EDEMA, NOS			1 (2%)
PLASMA-CELL INFILTRATE		1 (2%)	
ATROPHY, NOS		1 (2%)	2 (4%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	6 (13%)
HYPERPLASIA, LYMPHOID	3 (15%)	5 (10%)	
#THYMUS	(10)	(22)	(24)
HEMORRHAGE		1 (5%)	
ATROPHY, NOS	1 (10%)	7 (32%)	8 (33%)
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
MINERALIZATION		1 (2%)	
#HEART/ATRIUM	(20)	(50)	(50)
THROMBUS, ORGANIZED			1 (2%)
#AURICULAR APPENDAGE	(20)	(50)	(50)
THROMBUS, ORGANIZED		2 (4%)	1 (2%)
CALCIFICATION, DYSTROPHIC		1 (2%)	
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, CHRONIC	16 (80%)	40 (80%)	41 (82%)
#ENDOCARDIUM	(20)	(50)	(50)
FIBROSIS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(49)	(48)
INFLAMMATION, CHRONIC			1 (2%)
FIBROSIS, DIFFUSE			1 (2%)
#LIVER	(20)	(50)	(50)
CONGESTION, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		3 (6%)	1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
CHOLANGIOFIBROSIS	8 (40%)	5 (10%)	7 (14%)
NECROSIS, NOS	2 (10%)		1 (2%)
METAMORPHOSIS FATTY	1 (5%)	15 (30%)	11 (22%)
LIPOIDOSIS			1 (2%)
HYPERTROPHY, NOS	2 (10%)	2 (4%)	
HYPERPLASIA, NOS	6 (30%)	18 (36%)	12 (24%)
#PORTAL TRACT	(20)	(50)	(50)
FIBROSIS		1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(50)	(50)
LIPOIDOSIS	1 (5%)		
#BILE DUCT	(20)	(50)	(50)
INFLAMMATION, CHRONIC	5 (25%)	29 (58%)	24 (48%)
HYPERPLASIA, NOS	18 (90%)	47 (94%)	43 (86%)
#PANCREAS	(20)	(49)	(49)
PERIARTERITIS		6 (12%)	3 (6%)
#STOMACH	(20)	(50)	(50)
ULCER, ACUTE	1 (5%)		
#GASTRIC SUBMUCOSA	(20)	(50)	(50)
EDEMA, NOS	1 (5%)		
#COLON	(20)	(49)	(50)
HYPERPLASIA, LYMPHOID	2 (10%)		2 (4%)
#COLONIC SUBMUCOSA	(20)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (5%)		
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
MINERALIZATION		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	15 (75%)	38 (76%)	36 (72%)
NEPHROPATHY		1 (2%)	3 (6%)
HEMOSIDEROSIS			1 (2%)
#KIDNEY/CORTEX	(20)	(50)	(50)
CYST, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(49)	(49)
CYST, NOS	2 (11%)	4 (8%)	5 (10%)
HEMORRHAGIC CYST		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL	(20)	(50)	(50)
CONGESTION, NOS			1 (2%)
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(20)	(50)	(50)
LIPOIDOSIS		2 (4%)	1 (2%)
HYPERPLASIA, NOS		2 (4%)	4 (8%)
#THYROID	(19)	(50)	(48)
FOLLICULAR CYST, NOS	1 (5%)	1 (2%)	
HYPERPLASIA, C-CELL	3 (16%)	7 (14%)	9 (19%)
#PARATHYROID	(17)	(46)	(41)
HYPERPLASIA, NOS	1 (6%)	3 (7%)	
#PANCREATIC ISLETS	(20)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS			1 (2%)
GALACTOCELE	1 (5%)	5 (10%)	5 (10%)
LACTATION	15 (75%)	31 (62%)	37 (74%)
*PREPUTIAL GLAND	(20)	(50)	(50)
DILATATION, NOS		1 (2%)	
#PROSTATE	(20)	(48)	(49)
INFLAMMATION, ACUTE		5 (10%)	4 (8%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ABSCESS, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS, DIFFUSE			1 (2%)
ATROPHY, NOS	4 (20%)	8 (17%)	13 (27%)
HYPERPLASIA, NOS		2 (4%)	1 (2%)
HYPERPLASIA, FOCAL	2 (10%)	2 (4%)	1 (2%)
#TESTIS	(20)	(50)	(50)
ATROPHY, NOS	3 (15%)	16 (32%)	20 (40%)
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	
*EPIDIDYMIS	(20)	(50)	(50)
EDEMA, NOS			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
LIPOGRANULOMA		1 (2%)	
GRANULOMA, FOREIGN BODY		1 (2%)	
FIBROSIS, DIFFUSE	2 (10%)	9 (18%)	14 (28%)
ATROPHY, NOS		2 (4%)	3 (6%)
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(49)
HYDROCEPHALUS, NOS			2 (4%)
HEMORRHAGE	1 (5%)		
ATROPHY, PRESSURE	1 (5%)	1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
LIPOGRANULOMA			1 (2%)
HEMOSIDEROSIS			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
ATROPHY, NOS	14 (70%)	21 (42%)	17 (34%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED PHTHALAMIDE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
CYST, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(49)
CONGESTION, NOS			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(49)	(49)
HYPERPLASIA, GRANULOCYTIC	2 (11%)	4 (8%)	
HYPOPLASIA, ERYTHROID			1 (2%)
#SPLEEN	(20)	(50)	(49)
CONGESTION, NOS		1 (2%)	
HEMOSIDEROSIS	6 (30%)	6 (12%)	13 (27%)
ATROPHY, NOS	1 (5%)		2 (4%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
HEMATOPOIESIS		1 (2%)	
#MANDIBULAR L. NODE	(18)	(49)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#CERVICAL LYMPH NODE	(18)	(49)	(48)
LYMPHANGIECTASIS		3 (6%)	13 (27%)
HEMORRHAGE	1 (6%)		
PLASMA-CELL INFILTRATE		1 (2%)	
HEMOSIDEROSIS			2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, NOS	1 (6%)		
ERYTHROPHAGOCYTOSIS		1 (2%)	5 (10%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID		5 (10%)	3 (6%)
#LUMBAR LYMPH NODE	(18)	(49)	(48)
ERYTHROPHAGOCYTOSIS	1 (6%)		
#MESENTERIC L. NODE	(18)	(49)	(48)
CONGESTION, NOS			1 (2%)
ATROPHY, NOS		2 (4%)	4 (8%)
ERYTHROPHAGOCYTOSIS		2 (4%)	1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	2 (4%)
#RENAL LYMPH NODE	(18)	(49)	(48)
LYMPHANGIECTASIS			1 (2%)
HEMOSIDEROSIS	1 (6%)		
ERYTHROPHAGOCYTOSIS	1 (6%)		1 (2%)
#THYMUS	(18)	(31)	(23)
ATROPHY, NOS	15 (83%)	28 (90%)	20 (87%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, CHRONIC	9 (45%)	28 (56%)	25 (50%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(49)
HERNIA, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
CHOLANGIOFIBROSIS		7 (14%)	4 (8%)
NECROSIS, NOS		1 (2%)	1 (2%)
METAMORPHOSIS FATTY	1 (5%)	5 (10%)	1 (2%)
HYPERTROPHY, NOS		3 (6%)	2 (4%)
HYPERPLASIA, NOS	17 (85%)	40 (80%)	35 (71%)
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, C-CELL		1 (2%)	
#LIVER/KUPFFER CELL	(20)	(50)	(49)
PIGMENTATION, NOS		1 (2%)	
#BILE DUCT	(20)	(50)	(49)
INFLAMMATION, CHRONIC	1 (5%)	1 (2%)	3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	15 (75%)	40 (80%)	26 (53%)
#PANCREAS	(19)	(49)	(48)
PERIARTERITIS	1 (5%)	1 (2%)	1 (2%)
#PANCREATIC ACINUS	(19)	(49)	(48)
ATROPHY, NOS		1 (2%)	
#STOMACH	(20)	(50)	(49)
CYST, NOS	1 (5%)		
INFLAMMATION, ACUTE	1 (5%)		
INFLAMMATION, CHRONIC		1 (2%)	
#PEYERS PATCH	(20)	(50)	(48)
ULCER, CHRONIC		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#COLON	(20)	(50)	(48)
HYPERPLASIA, LYMPHOID	2 (10%)	4 (8%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
HYDRONEPHROSIS			2 (4%)
PYELONEPHRITIS, NOS			5 (10%)
INFLAMMATION, NOS			1 (2%)
PYELONEPHRITIS, ACUTE	1 (5%)		
INFLAMMATION, CHRONIC	1 (5%)	9 (18%)	14 (28%)
PYELONEPHRITIS, CHRONIC			4 (8%)
NEPHROPATHY			1 (2%)
#KIDNEY/MEDULLA	(20)	(50)	(50)
MINERALIZATION			2 (4%)
#KIDNEY/PELVIS	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL			2 (4%)
#URINARY BLADDER	(18)	(49)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS			2 (4%)
INFLAMMATION, ACUTE	1 (6%)		
INFLAMMATION, CHRONIC			5 (10%)
HYPERPLASIA, EPITHELIAL			7 (14%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#U. BLADDER/MUCOSA	(18)	(49)	(50)
CALCULUS, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(50)	(48)
CYST, NOS	7 (37%)	4 (8%)	4 (8%)
HEMORRHAGIC CYST	4 (21%)	3 (6%)	
#ADRENAL	(20)	(50)	(50)
FIBROSIS		1 (2%)	
ANGIECTASIS	4 (20%)	1 (2%)	4 (8%)
#ADRENAL CORTEX	(20)	(50)	(50)
NECROSIS, FOCAL			1 (2%)
LIPOIDOSIS		2 (4%)	3 (6%)
HYPERPLASIA, NOS			4 (8%)
#THYROID	(20)	(50)	(48)
HYPERPLASIA, C-CELL	4 (20%)	11 (22%)	9 (19%)
#PARATHYROID	(18)	(41)	(42)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
GALACTOCELE	1 (5%)	4 (8%)	11 (22%)
HYPERPLASIA, NOS			1 (2%)
LACTATION	17 (85%)	40 (80%)	28 (56%)
#UTERUS	(20)	(50)	(49)
POLYP, INFLAMMATORY	7 (35%)	10 (20%)	1 (2%)
#UTERUS/ENDOMETRIUM	(20)	(50)	(49)
CYST, NOS		2 (4%)	1 (2%)
INFLAMMATION, ACUTE VESICULAR		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)
#OVARY/PAROVARIAN	(20)	(50)	(49)
LIPOGRANULOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#OVARY	(20)	(50)	(49)
FOLLICULAR CYST, NOS	1 (5%)	2 (4%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(19)	(50)	(49)
HYDROCEPHALUS, NOS			1 (2%)
ABSCESS, NOS			1 (2%)
ATROPHY, PRESSURE		4 (8%)	3 (6%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED PHTHALAMIDE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED PHTHALAMIDE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
CONGESTION, NOS		2 (4%)	4 (8%)
HYPEREMIA		1 (2%)	1 (2%)
EDEMA, NOS		3 (6%)	1 (2%)
INFLAMMATION, NOS	1 (5%)		1 (2%)
INFLAMMATION, DIFFUSE	1 (5%)		1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(49)	(50)
ATROPHY, NOS			1 (2%)
ANGIECTASIS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)		5 (10%)
HEMATOPOIESIS		4 (8%)	3 (6%)
#SPLENIC FOLLICLES	(20)	(49)	(50)
NECROSIS, NOS			1 (2%)
#HEPATIC LYMPH NODE	(20)	(50)	(46)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(20)	(50)	(46)
CONGESTION, NOS	4 (20%)	6 (12%)	5 (11%)
HEMORRHAGE		1 (2%)	2 (4%)
HEMOSIDEROSIS			1 (2%)
ERYTHROPHAGOCYTOSIS	1 (5%)	1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, RETICULUM CELL	2 (10%)		1 (2%)
HYPERPLASIA, LYMPHOID	5 (25%)	5 (10%)	9 (20%)
HEMATOPOIESIS	9 (45%)	10 (20%)	11 (24%)
#RENAL LYMPH NODE	(20)	(50)	(46)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#THYMUS	(12)	(30)	(33)
CYST, NOS			3 (9%)
ATROPHY, NOS			1 (3%)
CIRCULATORY SYSTEM			
*MESENTERIC ARTERY	(20)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
*HEPATIC VEIN	(20)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
HERNIA INCOMPLETE			1 (2%)
CONGESTION, NOS	1 (5%)		
NECROSIS, NOS		4 (8%)	2 (4%)
NECROSIS, FOCAL	2 (10%)	1 (2%)	1 (2%)
LIPOIDOSIS	2 (10%)	5 (10%)	3 (6%)
#STOMACH	(19)	(49)	(49)
ULCER, FOCAL			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
#CARDIAC STOMACH	(19)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERKERATOSIS		1 (2%)	
#PEYERS PATCH	(20)	(49)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
HYDRONEPHROSIS		2 (4%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC		4 (8%)	1 (2%)
NEPHROPATHY	1 (5%)		1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)		
#KIDNEY/CORTEX	(20)	(50)	(50)
CYST, NOS		1 (2%)	1 (2%)
#KIDNEY/TUBULE	(20)	(50)	(50)
DILATATION, NOS			1 (2%)
LIPOIDOSIS		1 (2%)	
CYTOPLASMIC VACUOLIZATION	6 (30%)		2 (4%)
#KIDNEY/PELVIS	(20)	(50)	(50)
DILATATION, NOS			1 (2%)
#URINARY BLADDER	(20)	(46)	(48)
HEMORRHAGE			1 (2%)
CRYSTALS, NOS			3 (6%)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(17)	(48)	(42)
CYST, NOS			2 (5%)
#ADRENAL CORTEX	(20)	(49)	(45)
CYST, NOS	1 (5%)		
LIPOIDOSIS	1 (5%)		
HYPERPLASIA, NOS		5 (10%)	1 (2%)
#THYROID	(19)	(48)	(50)
FOLLICULAR CYST, NOS		2 (4%)	
#PARATHYROID	(10)	(21)	(26)
CYST, NOS	2 (20%)		
#PANCREATIC ISLETS	(20)	(50)	(49)
HYPERPLASIA, NOS	1 (5%)		
REPRODUCTIVE SYSTEM			
#PROSTATE	(19)	(48)	(44)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ABSCESS, NOS			1 (2%)
#TESTIS	(20)	(50)	(50)
ATROPHY, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE	(20)	(50)	(50)
OSTEOPOROSIS			1 (2%)
*ABDOMINAL MUSCLE	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
INFARCT, NOS		1 (2%)	
*PERITONEUM	(20)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
*MESENTERY	(20)	(50)	(50)
LIPOGRANULOMA	1 (5%)		2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
CONGESTION, NOS	1 (5%)		
HYPERPLASIA, LYMPHOID	1 (5%)		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	2

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
AUTO/NECROPSY/HISTO PERF			1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED PHTHALAMIDE IN THE DIET

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
ANIMALS MISSING			1	1	2
ANIMALS NECROPSIED	20	20	49	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	20	49	49	48
INTEGUMENTARY SYSTEM					
NONE					
RESPIRATORY SYSTEM					
#LUNG/BRONCHUS	(20)	(20)	(48)	(49)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (5%)			
HYPERPLASIA, LYMPHOID					2 (4%)
#LUNG	(20)	(20)	(48)	(49)	(48)
CONGESTION, NOS					1 (2%)
HYPEREMIA					2 (4%)
EDEMA, NOS					1 (2%)
PERIARTERITIS			1 (2%)		
HEMATOPOIETIC SYSTEM					
#BONE MARROW	(20)	(20)	(49)	(49)	(47)
HYPERPLASIA, NOS					1 (2%)
ERYTHROPOIESIS					1 (2%)
#SPLEEN	(19)	(20)	(49)	(49)	(48)
INFLAMMATION, ACUTE			1 (2%)		
ATROPHY, NOS					1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (5%)	7 (14%)	5 (10%)	7 (15%)
HEMATOPOIESIS	1 (5%)		1 (2%)	3 (6%)	4 (8%)
#SPLENIC RED PULP	(19)	(20)	(49)	(49)	(48)
HISTIOCYTOSIS				1 (2%)	
#CERVICAL LYMPH NODE	(20)	(20)	(48)	(47)	(47)
HYPERPLASIA, LYMPHOID					1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#LUMBAR LYMPH NODE	(20)	(20)	(48)	(47)	(47)
INFLAMMATION, ACUTE			1 (2%)		
#MESENTERIC L. NODE	(20)	(20)	(48)	(47)	(47)
CONGESTION, NOS	1 (5%)		3 (6%)	1 (2%)	2 (4%)
INFLAMMATION, GRANULOMATOUS				1 (2%)	
ATROPHY, NOS				1 (2%)	
HYPERPLASIA, LYMPHOID	4 (20%)	2 (10%)	7 (15%)	2 (4%)	4 (9%)
HEMATOPOIESIS			1 (2%)	1 (2%)	
#THYMUS	(11)	(17)	(43)	(37)	(43)
CYST, NOS	1 (9%)				
NECROSIS, NOS				1 (3%)	
ATROPHY, NOS				3 (8%)	8 (19%)
HYPERPLASIA, LYMPHOID				1 (3%)	6 (14%)
CIRCULATORY SYSTEM					
#MYOCARDIUM	(20)	(20)	(48)	(49)	(48)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)		
*RENAL ARTERY	(20)	(20)	(49)	(49)	(48)
DEGENERATION, NOS					1 (2%)
NECROSIS, NOS					1 (2%)
#HEPATIC SINUSOID	(20)	(20)	(49)	(49)	(48)
LEUKOCYTOSIS, NOS			1 (2%)		
DIGESTIVE SYSTEM					
#LIVER	(20)	(20)	(49)	(49)	(48)
NECROSIS, NOS	1 (5%)		2 (4%)	3 (6%)	
METAMORPHOSIS FATTY					1 (2%)
LIPOIDOSIS	1 (5%)	4 (20%)	2 (4%)	7 (14%)	2 (4%)
FOCAL CELLULAR CHANGE	1 (5%)		1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, RETICULUM CELL				1 (2%)	
HYPERPLASIA, LYMPHOID	2 (10%)		1 (2%)		
#LIVER/CENTRILOBULAR	(20)	(20)	(49)	(49)	(48)
LIPOIDOSIS			1 (2%)		
#LIVER/PERIPORTAL	(20)	(20)	(49)	(49)	(48)
LIPOIDOSIS					1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#LIVER/KUPFFER CELL	(20)	(20)	(49)	(49)	(48)
HYPERPLASIA, NOS		1 (5%)			
#PANCREAS	(20)	(20)	(47)	(49)	(48)
DILATATION/DUCTS	1 (5%)	1 (5%)			
#PANCREATIC ACINUS	(20)	(20)	(47)	(49)	(48)
ATROPHY, NOS	1 (5%)	2 (10%)			
#STOMACH	(20)	(20)	(49)	(48)	(48)
EPIDERMAL INCLUSION CYST					1 (2%)
ULCER, NOS					3 (6%)
ULCER, FOCAL					2 (4%)
#CARDIAC STOMACH	(20)	(20)	(49)	(48)	(48)
INFLAMMATION, ACUTE					2 (4%)
INFLAMMATION, ACUTE/CHRONIC		1 (5%)			
HYPERKERATOSIS					1 (2%)
#SMALL INTESTINE	(20)	(20)	(48)	(49)	(48)
HYPERTROPHY, NOS					1 (2%)
#PEYERS PATCH	(20)	(20)	(48)	(49)	(48)
HYPERPLASIA, LYMPHOID	1 (5%)		3 (6%)		1 (2%)
#COLON	(20)	(20)	(49)	(46)	(46)
NEMATODIASIS					1 (2%)
#COLONIC SEROSA	(20)	(20)	(49)	(46)	(46)
CYST, NOS	1 (5%)				
INFLAMMATION, CHRONIC				1 (2%)	
URINARY SYSTEM					
#KIDNEY	(20)	(20)	(49)	(49)	(48)
CALCULUS, NOS				2 (4%)	
HYDRONEPHROSIS		1 (5%)	1 (2%)	1 (2%)	3 (6%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)				
PYELONEPHRITIS, ACUTE					1 (2%)
PERIVASCULITIS					1 (2%)
NEPHROPATHY		2 (10%)		4 (8%)	14 (29%)
HYPERPLASIA, LYMPHOID	1 (5%)			1 (2%)	
#KIDNEY/CORTEX	(20)	(20)	(49)	(49)	(48)
MINERALIZATION					1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#RENAL PAPILLA	(20)	(20)	(49)	(49)	(48)
INFLAMMATION, NECROTIZING					1 (2%)
#KIDNEY/TUBULE	(20)	(20)	(49)	(49)	(48)
MINERALIZATION					2 (4%)
DILATATION, NOS					1 (2%)
NECROSIS, NOS					1 (2%)
*URETER	(20)	(20)	(49)	(49)	(48)
RETENTION FLUID					1 (2%)
#URINARY BLADDER	(20)	(20)	(48)	(46)	(44)
HEMORRHAGE					1 (2%)
INFLAMMATION, NOS				2 (4%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)				
CRYSTALS, NOS				5 (11%)	17 (39%)
HYPERPLASIA, EPITHELIAL				4 (9%)	3 (7%)
#U. BLADDER/MUCOSA	(20)	(20)	(48)	(46)	(44)
DYSPLASIA, NOS					1 (2%)
#U.BLADDER/SUBMUCOSA	(20)	(20)	(48)	(46)	(44)
EDEMA, NOS					7 (16%)
ENDOCRINE SYSTEM					
#PITUITARY	(20)	(18)	(46)	(47)	(41)
HEMORRHAGE					1 (2%)
#ADRENAL CORTEX	(20)	(20)	(49)	(49)	(47)
LIPOIDOSIS			1 (2%)		
HYPERPLASIA, NOS	1 (5%)	2 (10%)	2 (4%)		
#ZONA RETICULARIS	(20)	(20)	(49)	(49)	(47)
ATROPHY, NOS					1 (2%)
#THYROID	(20)	(19)	(46)	(47)	(48)
FOLLICULAR CYST, NOS	2 (10%)		1 (2%)		
REPRODUCTIVE SYSTEM					
#UTERUS	(20)	(20)	(48)	(47)	(46)
PYOMETRA				1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
POLYP, INFLAMMATORY		1 (5%)	1 (2%)		
#UTERUS/ENDOMETRIUM	(20)	(20)	(48)	(47)	(46)
CYST, NOS	10 (50%)	15 (75%)	21 (44%)	18 (38%)	12 (26%)
INFLAMMATION, ACUTE SUPPURATIVE					1 (2%)
HYPERPLASIA, CYSTIC			7 (15%)	5 (11%)	1 (2%)
#OVARY	(19)	(20)	(48)	(47)	(44)
CYST, NOS	3 (16%)	5 (25%)	9 (19%)	5 (11%)	5 (11%)
HEMORRHAGE		1 (5%)			
HEMORRHAGIC CYST		1 (5%)	1 (2%)		
CALCIFICATION, DYSTROPHIC					1 (2%)
NERVOUS SYSTEM					
NONE					
SPECIAL SENSE ORGANS					
*EYE/RETINA	(20)	(20)	(49)	(49)	(48)
ATROPHY, NOS					1 (2%)
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
*PERITONEUM	(20)	(20)	(49)	(49)	(48)
INFLAMMATION, SUPPURATIVE					1 (2%)
*MESENTERY	(20)	(20)	(49)	(49)	(48)
LIPOGRANULOMA	4 (20%)		4 (8%)	1 (2%)	
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(20)	(20)	(49)	(49)	(48)
HEMATOPOIESIS					1 (2%)
SPECIAL MORPHOLOGY SUMMARY					
NO LESION REPORTED	2	1	1	3	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	MID AND HIGH DOSE CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMAL MISSING/NO NECROPSY			1	1	2
AUTO/NECROPSY/HISTO PERF					1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED PHTHALAMIDE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalamide in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	3/20 (15)	3/50 (6)	0/50 (0)
P Values (c,d)	P = 0.010 (N)	N.S.	P = 0.021 (N)
Relative Risk (f)		0.400	0.000
Lower Limit		0.060	0.000
Upper Limit		2.802	0.659
Weeks to First Observed Tumor	93	106	--
Hematopoietic System: Lymphoma or Leukemia (b)	8/20 (40)	12/50 (24)	8/50 (16)
P Values (c,d)	P = 0.026 (N)	N.S.	P = 0.035 (N)
Relative Risk (f)		0.600	0.400
Lower Limit		0.280	0.161
Upper Limit		1.471	1.073
Weeks to First Observed Tumor	91	79	91

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	3/18 (17)	4/49 (8)	1/49 (2)
P Values (c,d)	P = 0.031 (N)	N.S.	N.S.
Relative Risk (f)		0.490	0.122
Lower Limit		0.095	0.002
Upper Limit		3.118	1.435
Weeks to First Observed Tumor	106	97	106
Pituitary: Chromophobe Carcinoma (b)	1/18 (6)	2/49 (4)	8/49 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.735	2.939
Lower Limit		0.042	0.448
Upper Limit		42.478	127.379
Weeks to First Observed Tumor	106	106	98

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Carcinoma or Adenoma (b)	4/18 (22)	18/49 (37)	17/49 (35)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.653	1.561
Lower Limit		0.660	0.616
Upper Limit		6.011	5.720
Weeks to First Observed Tumor	93	94	91
Adrenal: Pheochromocytoma (b)	4/20 (20)	11/50 (22)	11/50 (22)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.100	1.100
Lower Limit		0.384	0.384
Upper Limit		4.321	4.321
Weeks to First Observed Tumor	104	83	96

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma or Carcinoma (b)	0/19 (0)	4/50 (8)	6/48 (13)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.368	0.662
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	99	98
Testis: Interstitial-cell Tumor (b)	1/20 (5)	3/50 (6)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.200	1.200
Lower Limit		0.106	0.106
Upper Limit		61.724	61.724
Weeks to First Observed Tumor	78	83	86

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor, Malignant (b)	17/20 (85)	41/50 (82)	37/50 (74)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.965	0.871
Lower Limit		0.802	0.719
Upper Limit		1.310	1.224
Weeks to First Observed Tumor	97	96	90

(a) Dosed groups received 15,000 or 30,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent)

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalamide in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	5/20 (25)	5/50 (10)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.400	0.480
Lower Limit		0.107	0.143
Upper Limit		1.583	1.807
Weeks to First Observed Tumor	80	78	101
Liver: Neoplastic Nodule (b)	2/20 (10)	2/50 (4)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.400	1.225
Lower Limit		0.032	0.248
Upper Limit		5.278	11.804
Weeks to First Observed Tumor	106	106	106

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	3/19 (16)	2/50 (4)	1/48 (2)
P Values (c,d)	P = 0.040 (N)	N.S.	N.S.
Relative Risk (f)		0.253	0.132
Lower Limit		0.023	0.003
Upper Limit		2.077	1.547
Weeks to First Observed Tumor	80	76	80
Pituitary: Adenocarcinoma, NOS (b)	0/19 (0)	3/50 (6)	1/48 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.238	0.022
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	95	106

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Carcinoma or Adenoma (b)	5/19 (26)	25/50 (50)	24/48 (50)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.900	1.900
Lower Limit		0.876	0.872
Upper Limit		5.526	5.528
Weeks to First Observed Tumor	103	104	98
Thyroid: C-cell Adenoma (b)	1/20 (5)	5/50 (10)	2/48 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.000	0.833
Lower Limit		0.249	0.047
Upper Limit		92.596	48.155
Weeks to First Observed Tumor	106	95	106

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Cystadenoma, NOS (b)	0/20 (0)	1/50 (2)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.022	0.250
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	106	106
Mammary Gland: Fibroadenoma (b)	3/20 (15)	10/50 (20)	9/50 (18)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.333	1.200
Lower Limit		0.398	0.346
Upper Limit		7.002	6.408
Weeks to First Observed Tumor	106	106	99

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalamide in the Diet (a)

(continued)

(a) Dosed groups received 5,000 or 10,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent)

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED PHTHALAMIDE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phthalamide in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	3/20 (15)	7/50 (14)	10/50 (20)
P Values (c,d)	N.S.	N.S	N.S.
Relative Risk (f)		0.933	1.333
Lower Limit		0.245	0.398
Upper Limit		5.215	7.002
Weeks to First Observed Tumor	105	105	102
Hematopoietic System: Lymphoma (b)	2/20 (10)	9/50 (18)	9/50 (18)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.800	1.800
Lower Limit		0.426	0.426
Upper Limit		16.255	16.255
Weeks to First Observed Tumor	105	88	92

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangioma (b)	0/20 (0)	4/50 (8)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.386	0.250
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105
All Sites: Hemangiosarcoma (b)	1/20 (5)	0/50 (0)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	1.200
Lower Limit		0.000	0.106
Upper Limit		7.475	61.724
Weeks to First Observed Tumor	105	--	78

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangioma or Hemangiosarcoma (b)	1/20 (5)	4/50 (8)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.600	2.400
Lower Limit		0.175	0.325
Upper Limit		77.169	108.021
Weeks to First Observed Tumor	105	105	78
Liver: Hepatocellular Carcinoma (b)	8/20 (40)	12/50 (24)	9/50 (18)
P Values (c,d)	P = 0.045 (N)	N.S.	N.S.
Relative Risk (f)		0.600	0.450
Lower Limit		0.280	0.190
Upper Limit		1.471	1.174
Weeks to First Observed Tumor	99	80	96

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Heptocellular Carcinoma or Adenoma (b)	9/20 (45)	17/50 (34)	13/50 (26)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.756	0.578
Lower Limit		0.404	0.289
Upper Limit		1.639	1.316
Weeks to First Observed Tumor	99	80	96
Pancreatic Islets: Islet-cell Adenoma (b)	2/20 (10)	1/50 (2)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.200	1.224
Lower Limit		0.004	0.248
Upper Limit		3.681	11.802
Weeks to First Observed Tumor	105	105	105

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phthalamide in the Diet (a)

(continued)

(a) Dosed groups received 25,000 or 50,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent)

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phthalamide in the Diet (a)

Topography: Morphology	Combined Control	Low Dose	Mid Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	3/40 (8)	5/48 (10)	1/49 (2)	0/48 (0)
P Values (c,d)	P = 0.024* (N) N.S.**	N.S.	N.S.	N.S.
Relative Risk (f)		1.389	0.272	0.000
Lower Limit		0.290	0.005	0.000
Upper Limit		8.481	3.241	1.382
Weeks to First Observed Tumor	103	79	101	--
Hematopoietic System: Lymphoma or Leukemia (b)	7/40 (18)	12/49 (24)	17/49 (35)	3/48 (6)
P Values (c,d)	P = 0.042** N.S.*	N.S.	N.S.	N.S.
Departure From Linear Trend (e)	P = 0.007*			
Relative Risk (f)		1.399	1.983	0.357
Lower Limit		0.566	0.897	0.063
Upper Limit		3.817	5.087	1.454
Weeks to First Observed Tumor	61	74	73	101

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Combined Control	Low Dose	Mid Dose	High Dose
All Sites: Hemangioma (b)	2/40 (5)	3/49 (6)	1/49 (2)	0/48 (0)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (f)		1.224	0.408	0.000
Lower Limit		0.148	0.007	0.000
Upper Limit		14.113	7.568	2.812
Weeks to First Observed Tumor	103	97	105	--
All Sites: Hemangioma or Hemangiosarcoma (b)	2/40 (5)	3/49 (6)	3/49 (6)	0/48 (0)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (f)		1.224	1.224	0.000
Lower Limit		0.148	0.148	0.000
Upper Limit		14.113	14.113	2.812
Weeks to First Observed Tumor	103	97	105	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phthalamide in the Diet (a)

(continued)

Topography: Morphology	Combined Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma (b)	4/40 (10)	2/49 (4)	2/49 (4)	0/48 (0)
P Values (c,d)	P = 0.030* (N) N.S.**	N.S.	N.S.	P = 0.039 (N)
Relative Risk (f)		0.408	0.408	0.000
Lower Limit		0.039	0.039	0.000
Upper Limit		2.697	2.697	0.896
Weeks to First Observed Tumor	78	103	105	--
Pituitary: Adenoma, NOS (b)	7/38 (18)	11/46 (24)	5/47 (11)	3/41 (7)
P Values (c,d)	P = 0.038* (N) N.S.**	N.S.	N.S.	N.S.
Relative Risk (f)		1.298	0.578	0.397
Lower Limit		0.514	0.157	0.071
Upper Limit		3.577	1.946	1.602
Weeks to First Observed Tumor	103	100	105	105

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phthalamide in the Diet (a)

(continued)

(a) Dosed groups received 6,200, 12,500, or 25,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test using combined control, low-, mid- and high-dose groups (*) and using combined control, low- and mid-dose groups (**) when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

Review of the Bioassay of Phthalamide* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

December 13, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute on the Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, and State health officials. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Phthalamide.

The reviewer for the report on the bioassay of Phthalamide agreed with the conclusion that the compound was not carcinogenic under the conditions of test. After a brief description of the experimental design, he noted that the weight depression "was not particularly impressive" among the treated high-dose animals. Based on the results of the study, he said that the compound did not appear to pose a carcinogenic risk to human beings. The reviewer moved that the report on the bioassay of Phthalamide be accepted as written. The motion was seconded and approved without objection.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical USA
Michael Shimkin, University of California at San Diego

Louise Strong, University of Texas Health Sciences Center
Kenneth Wilcox, Michigan State Health Department

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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